CLINICAL EVALUATION:
GINKGO BILOBA PREVENTION TRIAL IN OLDER INDIVIDUALS

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
National Center for Complementary
and Alternative Medicine
National Institutes of Health
Bethesda, Maryland 20892-2182
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May 15, 1999

Manufacturers of *Ginkgo biloba*

The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute on Aging (NIA), National Institutes of Health (NIH) are interested in cosponsoring a clinical evaluation of *Ginkgo biloba* for preventing the onset of dementia and or cognitive decline in older individuals (RFA: AT-99-001). The trial will investigate the safety and efficacy of *Ginkgo biloba* in individuals currently free of dementia compared to a placebo control. The clinical trial will be administered through NCCAM and additional scientific input provided by NIA.

The purpose of this letter is to inform interested parties that the NIH is interested in obtaining information (see attached: INFORMATION REQUIRED FROM THE MANUFACTURER) on available *Ginkgo biloba* products that are free from other bioactive ingredients and matching placebo for use in the clinical trial of *Ginkgo biloba* at no cost to the government. Costs for the conduct of the trial itself will be funded by the NCCAM through an NIH cooperative agreement mechanism. The NIH is not interested in promoting or supporting a specific marketing advantage of any one product over another; however, it is likely that only one collaborator or commercial product will be selected for this evaluation.

It is important that the *Ginkgo biloba* for the clinical trial be of high quality. The manufacturer must be prepared to provide adequate information about the source, collection, storage, processing, extraction and purification process, formulation, bioavailability, stability and safety of the product in order for the NIH to meet Food and Drug Administration (FDA) requirements for the filing of an Investigational New Drug Application (IND). The suppliers of *Ginkgo biloba* for the NIH study will be asked to enter into a Clinical Trial Agreement with the government which commits the supplier to provide formulated products of consistent quality and sufficient quantity for the completion of the clinical program. A copy of a model clinical trials agreement is available upon request. The agreement details the obligations of the government as the clinical trial sponsor and the company as the supplier of the *Ginkgo biloba*.

The agreement provides for:

1. The opportunity of the company to comment on the final clinical protocol.
2. The company to receive a copy of all adverse event reports as they are submitted to the FDA.
3. Obligations of the company to supply enough product and matching placebo for the completion of the trial as agreed upon.
4. Assurance of confidentiality of company proprietary information.
5. Exclusive access to the primary data from the clinical trial on its completion for regulatory purposes.

Please note that the *Ginkgo biloba* product will be distributed to the clinical sites by the NIH or the trial coordinating center at no cost to the company.

Under the agreement there will be no advertising or promotion of product efficacy until release of the clinical trial results by the NIH. The results of the clinical trial data will be released to the company 48 hours prior to the official report by the NIH.

We request that the materials be sent to the following address by 5:00 P.M. EDT July 1, 1999:

Richard L. Nahin, Ph.D., M.P.H.
Division of Extramural Research, Review and Training
National Center for Complementary
and Alternative Medicine
National Institutes of Health
9000 Rockville Pike
Bldg. 31, Room 5B-38
Bethesda, MD 20892-2182

If you would like a confidentiality agreement with the NIH prior to submitting the requested information please telephone Mr. Patrick Williams, Executive Officer, NCCAM, at (301) 594-2015. All information supplied will be kept in the strictest confidence and shared only with scientific reviewers who have signed a confidentiality agreement. We would appreciate a letter authorizing NIH staff involved in this project to access nonconfidential, nonproprietary information that you might have filed with the FDA. We look forward to receiving the requested information (see attached: INFORMATION REQUIRED FROM THE MANUFACTURER).

This letter is being sent to several companies and organizations and will also be available on the NCCAM and NIA home pages: http://altmed.od.nih.gov/nccam and http://www.nih.gov/nia.

Sincerely,

/S/

Richard L. Nahin, MPH, Ph.D.
Division of Extramural Research

National Center for Complementary
And Alternative Medicine

/S/

Neil Buckholtz, Ph.D..
Neuroscience and Neuropsychology of Aging Program
National Institute on Aging

INFORMATION REQUIRED FROM THE MANUFACTURER

The manufacturer of formulated *Ginkgo biloba* and matching placebo is asked to provide the following:

1. Preclinical and/or clinical and safety data suggesting efficacy of your product for treating or preventing dementia. Additionally, any available human absorption, distribution, metabolism and excretion data.

2. A copy of an Investigator Brochure for the product that includes safety information, published studies of *Ginkgo biloba* and a list of published studies conducted with your product.

3. A list of the countries where your product is in clinical testing or has been approved or marketed, if appropriate.

4. Whether there is an IND or Drug Master File (DMF) on file with the United States Food and Drug Administration (FDA). Please indicate when you filed the application and the current status of the IND or DMF. If you do not have an IND or DMF currently on file with the FDA, please indicate whether you will agree to submit sufficient and appropriate Chemistry, Manufacturing and Controls (CMC) documentation so that an IND can be filed either by you or by the trial Principal Investigator.

5. Identification of the sources of the *Ginkgo biloba* and assurance that the supply has not been placed on the FDA alert list.

6. Composition of the formulated product and the matching placebo to comply with new FDA labeling requirements for dietary supplements.

7. Details of the manufacturing facilities, process, process control, characterization and testing.

8. A complete Certificate of Analysis of the product showing: a) how the material is identified and its identity ensured from lot to lot; b) an HPLC profile or other suitable chromatographic profile or method for the characterization and standardization of the product; c) evidence of lot to lot consistency, potency, homogeneity and stability including an impurity profile; and d) information as to the product's safety and freedom from adventitious agents. The Certificate of Analysis should be of sufficient detail to be acceptable to the FDA for the filing of an IND.

9. Assurance that the formulated product and matching placebo are manufactured in compliance with current Good Manufacturing Practices (cGMP).

If selected for further clinical collaboration the following information would be required:

10. Manufactures should provide information on the product such as tablet or capsule size or other physical state , number of tablets/capsules or teaspoons per dose and number of doses/person required for the duration of treatment.

11. Information on the product packaging (number of tablets/capsules or teaspoons of powder per bottle and product label). For this initial inquiry, manufactures should assume that the trial dose will be 240 mg/day for three years. However, the final dose will not be decided until the first meeting of the trial steering committee.

12. Information on formulated product stability under the conditions of the manufacturer-recommended shipping and storage conditions. In particular, will a single batch of product be stable for the entire 3-5 year study? If not, how many batches will be required?

13. The supplier should note whether the product will be manufactured as a single lot or multiple lots.

14. The manufacturer must be able to supply sufficient quantity of the formulated *Ginkgo biloba* and matching placebo within proposed specifications for the duration of the clinical trial. These products should be provided in NIH approved packaging with labeling suitable for human double-blinded clinical trials. Depending on the shelf life of the products, the manufacturer may have to supply several batches distributed across the length of the trial.

15. Please indicate when the appropriately packaged final formulation of *Ginkgo biloba* can be made available to the NIH for use in the clinical study. Please indicate the exact date.

16. A plan for providing additional supplies of *Ginkgo biloba* at a later date, if necessary.

17. Instructions for use (ingestion, before during or after meals), interactions with concomitant medications and any known adverse experiences.